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Characterization of different reverse micelle interfaces using the reaction of 4-fluoro-3-nitrobenzoate with piperidine[†]

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ABSTRACT: The characterization of different reverse micellar interfaces, benzene–sodium 1,4-bis-2-ethylhexylsulfosuccinate (AOT)–water and benzene–benzyl-*n*-hexadecyldimethylammonium chloride (BHDC)–water, were studied using an aromatic nucleophilic substitution reaction, S_NAr, between acid 4-fluoro-3-nitrobenzoic (FNBA) and piperidine. The reaction was also studied in homogeneous media, water and benzene, varying the ionic strength in the aqueous solution. The kinetic profiles were investigated as a function of variables such as surfactant, amine concentration and the amount of water dispersed in the reverse micelles, $W_0 = [\text{water}]/[\text{surfactant}]$. In the pure solvents, water and benzene, there is no genuine base-catalyzed reaction. In water the reaction is faster than in benzene, owing to the better stabilization of the intermediate **Z**. Also, the reaction rate in water is accelerated by the addition of salt. In both micellar systems FNBA is totally incorporated in the interface of the aggregate because, under the working conditions of excess of amine, it is ionized to carboxylate, The reactions kinetics in these media can be quantitatively explained taking into account the distribution of the nucleophile between the bulk solvent and the micelle interfaces. In the AOT reverse micelles at $W_0 = 10$, the anionic substrate seems to be located in the water side of the interface whereas in BHDC it resides in the oil side of the interface. The results were used to evaluate the intrinsic second-order rate coefficient of the S_NAr reaction at the interface. From these data, properties such as micropolarity and ionic strength of this environment can be deduced. Hence, as expected, the micropolarity of the reverse micelles systems is higher than that of pure benzene and increases upon water addition. In the AOT system and owing to the location of the probe, the average ionic strength of the AOT reverse micelles could be estimated and a value of around 4.5 M was found. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: reverse micelles; AOT; aromatic nucleophilic substitution reaction; ionic strength

INTRODUCTION

Chemical reactivity in reverse micelles systems is an attractive object of study because these media are macroscopically homogeneous and isotropic, although they are heterogeneous on the molecular scale. These systems contain aqueous microdroplets entrapped in a film of surfactants and dispersed in a low-polarity bulk solvent.[1–6] It is also known that the physical characteristics of the water in the microdroplets differ from those of bulk water, mainly as regards mobility, polarity and properties affected by its high ionic strength and by the electronic influence of the charged surfactant heads.[5–8]

Two differentiated aqueous and organic pseudophases present in reversed micelles allow compartmentalization of solubilized species at the microscopic level. Solubilization of a reactant in the same region of the surfactant assembly can lead to significant acceleration of reaction rates, whereas the rates of reactions of segregated reactants are retarded. When reactants are in the water droplet, they are concentrated as in a nanoreactor, and since the size of this reactor is easily varied, the influence of the properties of the micellar system is relatively easy to assess.[9,10] On the other hand, reverse micellar systems are of interest as reaction media because they are powerful models for biological systems.[11–13]

Systematic studies using neutral nucleophiles in this kind of system are scarce. In previous work, we have been interested in the influence of cationic and anionic reverse micelles on the bimolecular aromatic nucleophilic substitution (S_NAr) reactions between halo nitro-substituted aromatic substrates and aliphatic amines. The results showed that the reactions are faster in the

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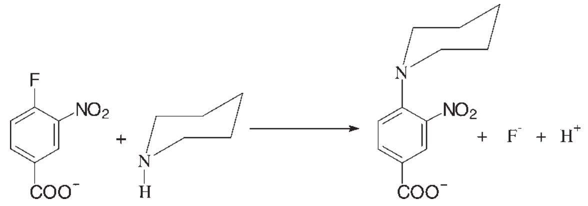
micellar media than in the pure solvent, being base catalyzed in the organic solvents but not in the reverse micelles.[14–16]

The aim of this work was to characterize two anionic and cationic reverse micelles interfaces, namely benzene–sodium 1,4-bis-2-ethylhexylsulfosuccinate (AOT)–water and benzene–benzyl-*n*-hexadecyldimethylammonium chloride (BHDC)–water, using the S_NAr reaction between acid 4-fluoro-3-nitrobenzoic (FNBA) and piperidine (PIP). Substrates containing carboxylic groups can be conveniently anchored in the reverse micelle systems. These types of substrate were used to evaluate the effect of the micellar orientation in direct micelles systems on the S_NAr reaction with hydroxide ion.[17,18] These studies discriminate between substrates with reaction center at the micellar water interface, where it is better situated for the substitution, and those with the reaction center that are more deeply buried in the micellar interior.

It is also known that in S_NAr reactions with electrically neutral nucleophilic reagents, e.g. amines, specific salt effects enhance the reaction rate.[19,20] Bimolecular reactions studied in micelles can be used to estimate the local concentration of ions at the interface, by using the rate constants in the micellar pseudophase. The majority of these studies were performed in direct micelles,[21,22] where it was shown that the interfacial ion concentration is different from that in the bulk. On the other hand, the literature in this respect for reverse micelles is scarce. For instance, Das *et al.*,[23] based on a modified phenyl cation-trapping protocol, showed that the local molar concentrations of bromide counter ions inside the water pool of cetyltrimethylammonium bromide (CTAB)–isooctane–*n*-hexanol–water reverse micelles decrease from 1.9 to 0.29 M as W_0 increases from 12 to 44, with a concomitant increase in the local water pool concentration of water from 43.8 to 55.4 M. Also, Cuccovia *et al.*,[24] by using chemical trapping, determined in reverse micelles of CTAB in *n*-dodecane–$CHCl_3$ and isooctane–*n*-hexanol, the bound bromide concentration, which decreases with W_0 and its value depends on the organic solvent and co-solvent. In this paper, it is shown that the kinetic results of the S_NAr reaction between amines and FNBA, which is totally incorporated at the aggregate interfaces, can be used to estimate the ionic strength of reverse micellar pseudophases.

RESULTS

The reaction of FNBA with PIP in homogeneous media, benzene and water, and in reverse micelles, benzene–AOT–water and benzene–BHDC–water, produces the corresponding *ipso*-fluorine substitution product [Eqn (1)] in quantitative yields, as shown by UV–visible spectroscopic analysis of the reaction mixture.



(1)

It should be noted that because the reactions are performed in excess of amine, FNBA is always present as carboxylate [the pirimidinium ion is not shown in Eqn (1) for the sake of clarity].

All the reactions follow pseudo-first-order kinetics. The spectra at different times of reaction show a clear isosbestic point, indicating the cleanness of the reactions. However, considering that hydroxide ion may result from amine hydrolysis in the water pool, the possibility of the reaction between FNBA and this ion was examined, but no reaction was detected under these experimental conditions.

In trying to elucidate the mechanism of the S_NAr reaction and to compare the homogeneous and microheterogeneous media, the influences of several variables were investigated as follows.

Reaction in benzene and water

The kinetic results are shown in Fig. 1(A). As can be inferred, the reaction rates increase with increasing amine concentration, being faster in water than benzene. In both cases a linear behavior was observed. It must be mentioned that the results in water are almost identical either considering the analytical PIP concentration or calculating it taking into account the hydrolysis basic-equilibrium ($pK_b = 2.88$).[25] This negligible protonation effect is due to the high amine concentration used in these experiments.

The effect of the ionic strength on this reaction was analyzed in water at [PIP] = 0.1 M, for [$NaNO_3$] in the range 0–5 M. The results are showed in Fig. 1(B). As it

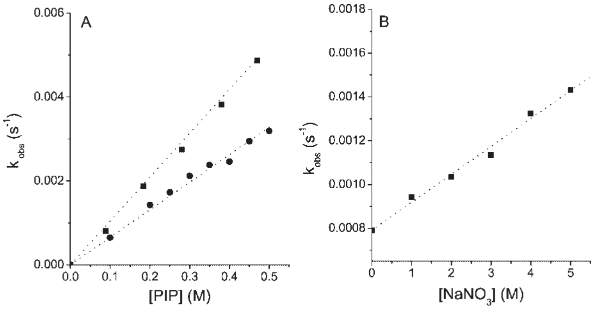


Figure 1. Dependence of k_{obs} on PIP concentration for the reaction between FNBA and PIP in (A) water (■) and benzene (●) $[FNBA] = 1.5 \times 10^{-4}$ M. (B) Dependence of k_{obs} on $NaNO_3$ concentration. $[FNBA] = 1.5 \times 10^{-4}$ M; [PIP] = 0.1 M

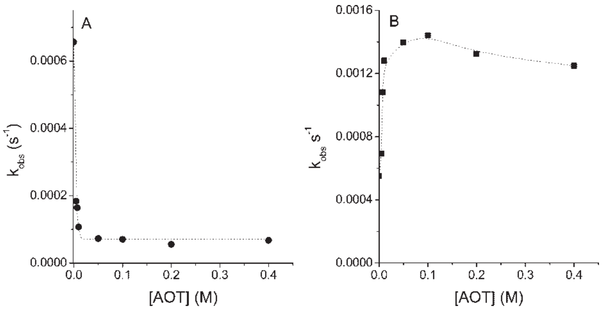


Figure 2. Dependence of k_{obs} on AOT concentration for the reaction between FNBA and PIP in water–AOT–benzene reverse micelles at (A) $W_0 = 0$ and (B) $W_0 = 10$. [FNBA] = 1.5×10^{-4} M; [PIP] = 0.1 M

can be observed, the reaction rate increases with increasing ionic strength, owing to the stabilization of the transition state, as was observed previously for similar S_NAr reactions.[19,20]

Reaction in the AOT–benzene system

Effects of AOT concentration

The kinetics of the reaction was studied varying [AOT] between 0 and 0.4 M, keeping the other experimental conditions fixed. Figure 2(A) shows the kinetic results at $W_0 = 0$. As can be observed, there is a sharp decrease in k_{obs} with increase in AOT concentration, reaching a constant value beyond [AOT] ≈ 0.05 M. On the other hand, at $W_0 = 10$, in the same surfactant range, there is a very rapid increase in k_{obs} with increase in [AOT] [Fig. 2(B)]. At [AOT] > 0.05 M, there is practically no variation of the reaction rate.

Effect of amine concentration

To study the effect of amine concentration, the reaction was carried out using 0.2 M AOT at $W_0 = 0$ and 10. The results are shown in Fig. 3(A) and (B), respectively. In both cases, k_{obs} increases linearly with increase in PIP concentration. The results show that the reaction is faster at high water content, as was observed by varying [AOT].

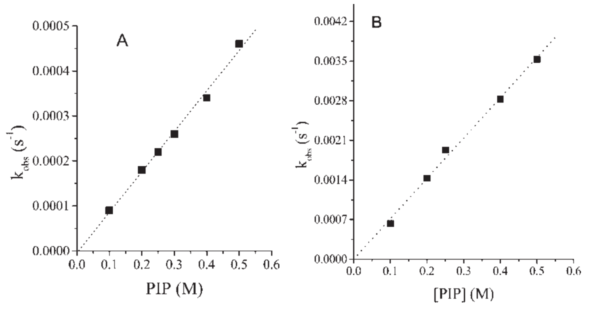


Figure 3. Variation of k_{obs} with PIP concentration for the reaction between FNBA and PIP in water–AOT–benzene reverse micelles at (A) $W_0 = 0$ and (B) $W_0 = 10$. [FNBA] = 1.5×10^{-4} M; [AOT] = 0.2 M. The dotted line shows the fitting by Eqn (8)

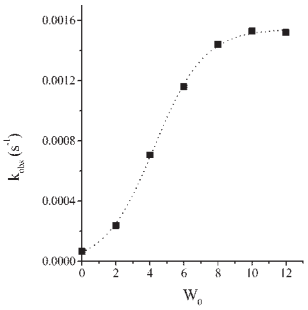


Figure 4. Variation of k_{obs} with W_0 in water–AOT–benzene reverse micelles for the reaction of FNBA with PIP. [FNBA] = 1.5×10^{-4} M; [PIP] = 0.1 M; [AOT] = 0.2 M

Effect of water dispersed

The effects of changing the value of W_0 on k_{obs} keeping the AOT and PIP concentrations constant is shown in Fig. 4. As can be observed, k_{obs} increases as W_0 increases until it reaches a constant value at $W_0 \approx 10$.

Reaction in benzene–BHDC–water reverse micelles

Effect of BHDC concentration

Typical kinetic results with varying BHDC concentration are shown in Fig. 5 for $W_0 = 0$ and 10. As can be observed, at $W_0 = 0$, k_{obs} decreases sharply with increasing BHDC concentration, reaching a constant value at [BHDC] > 0.05 M. On the other hand, at $W_0 = 10$ only a small increase in k_{obs} is observed, and also the reaction rate is constant at [BHDC] > 0.05 M.

Effect of amine concentration

Figure 6 shows the variation of k_{obs} with PIP concentration in the micelle at [BHDC] = 0.2 M, at $W_0 = 0$ and 10. At both values of W_0, there is a linear dependence between k_{obs} and the amine concentration. As was found previously in a similar S_NAr reaction with PIP as nucleophile, the reaction is faster at higher water content.[14]

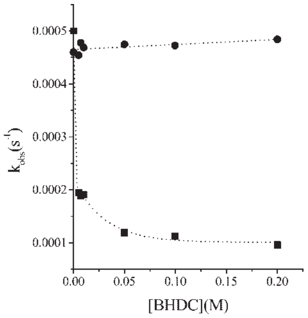


Figure 5. Dependence of k_{obs} on BHDC concentration for the reaction between FNBA and PIP in water–BHDC–benzene reverse micelles at $W_0 = 0$ (■) and $W_0 = 10$ (●). [FNBA] = 1.5×10^{-4} M; [PIP] = 0.1 M

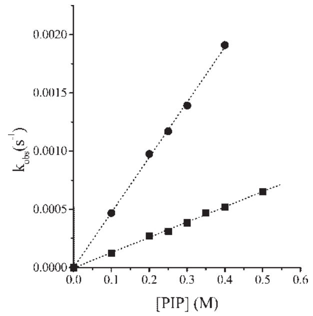


Figure 6. Variation of k_{obs} with PIP concentration for the reaction between FNBA and PIP in water–BHDC–benzene reverse micelles at $W_0 = 0$ (■) and $W_0 = 10$ (●). [FNBA] $= 1.5 \times 10^{-4}$ M; [BHDC] $= 0.2$ M. The dotted line shows the fitting by Eqn (8)

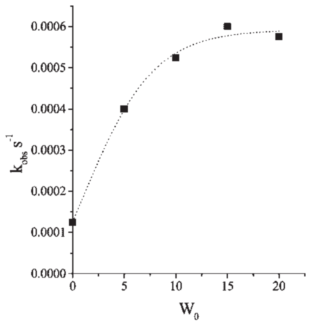


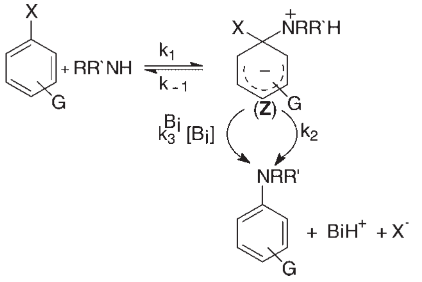
Figure 7. Variation of k_{obs} with W_0 in water–BHDC–benzene reverse micelles for the reaction of FNBA with PIP. [FNBA] $= 1.5 \times 10^{-4}$ M; [PIP] $= 0.1$ M; [BHDC] $= 0.2$ M

Effect of the water dispersed

The effect of increasing the water content is shown in Fig. 7. As can be observed, this tendency is similar to that found in the AOT system (Fig. 4). The rate of reaction is faster at higher W_0, reaching a constant value at $W_0 > 10$.

DISCUSSION

For primary or secondary amines as nucleophiles, the accepted general mechanism[20,26,27] for S_NAr reactions, involving halogen or nitrite as leaving groups, can be represented by Eqn (2).



(2)

where R′ could be H or an alkyl group, X is the leaving group, G represents electron-withdrawing substituents and B_i is the nucleophile or any other base added to the reaction medium. Application of the steady-state hypothesis to this mechanism, and in the limiting situation when $k_{-1} \gg k_2 + k_3^{B_i}$ [B_i], the following equation is obtained:

$$k_{obs}/[B_i] = k_A = k' + k''[B_i] \qquad (3)$$

where k_{obs} is the observed pseudo-first-order rate constant, k_A is the second-order rate constant, $k' = k_1k_2/k_{-1}$ and $k'' = k_1k_3^{B_i}/k_{-1}$. In this case the decomposition of **Z** is rate limiting and base catalysis may be expected. A linear response to base concentration such as depicted in Eqn (3) is characteristic of the majority of base-catalyzed reactions. On the other hand, if $k_{-1} \ll k_2 + k_3^{B_i}$ [B_i] or, more precisely, $k_2 \gg k_{-1}$, the formation of the intermediate **Z** is rate limiting and consequently $k_A = k_1$ and a plot of k_{obs} vs [B_i] gives a linear response.[20,26,27]

Figure 1 shows a linear dependence between k_{obs} and [PIP] in benzene and water. Therefore, according to Eqn (3), there is no genuine base-catalyzed reaction in both pure solvents. From the linear regression (Fig. 1, dotted lines) the values of $(6.6 \pm 0.2) \times 10^{-3}$ and $(1.1 \pm 0.1) \times 10^{-2}\,s^{-1}\,M^{-1}$ were found for k' in benzene and water, respectively. Thus, the formation of the **Z** intermediate is the rate-limiting reaction in both solvents. It must be noted that the reaction between 1-fluoro-2,4-dinitrobenzene with PIP in benzene is wholly base catalyzed.[28] On the other hand, in the same system but using 1-fluoro-2-nitrobenzene as substrate, the reaction is not base catalyzed.[20] Therefore, it can be inferred that the carboxylate group in FNBA is a poor electron-withdrawing substituent compared with the nitro group, the formation of the **Z** intermediate being the rate-determining step. As expected, enhancing the polarity of the solvent produces an increase in the reaction rate ($k'_{water}/k'_{benzene} \approx 2$) owing to the better stabilization of the transition state leading to this intermediate. It could be argued that the differences with benzene are not large, but it should be taken into account that in water the nucleophilicity of the amines is diminished by solvation of the nucleophile,[15] counteracting the effect of the intermediate stabilization.

According to the results and considering that only two pseudophases, the interface and the bulk organic solvent, are mainly present at $W_0 = 0$ and 10 and taking into account the amine distribution between these two environments, a mechanism summarized in Scheme 1 can be proposed:[2,5,14,15]

$$\begin{tikzcd} \text{FNBA} + \text{PIP}_b \arrow[r, shift left, "k_1^b"] \arrow[d, shift left, "K_A"] & Z_b \arrow[l, shift left, "k_{-1}^b"] \arrow[r, "k_2^b"] & P \\ \text{PIP}_f \arrow[u, shift left, "\text{Surf}"] & & \end{tikzcd}$$

Scheme 1

where the subscripts f and b indicate the organic phase and the micellar pseudophase, respectively, and Surf represents the total surfactant concentration. The rate coefficients of the reaction k_1, k_{-1} and k_2, were defined in Eqn (1). K_A is the distribution constant for PIP between the organic phase and micellar pseudophase. As mentioned previously, under the experimental conditions the carboxylic acid group of the substrate is ionized, forming an ion pair with the amine. In this way, the salt is mainly dissolved in a polar microenvironment (the interface)[17] and its distribution constant is not taken into account in Scheme 1. Moreover, this implies that the reaction occurs only in the micellar interior.

The micropolarity of the interface in reversed micelles of benzene–AOT or BHDC–water is always higher that in benzene.[8,29] Assuming that the reactions of FNBA with PIP are not base catalyzed in either the or the cationic anionic micellar interface, the formation of the intermediate $\mathbf{Z}_b$ is rate limiting. The linear relationships of k_{obs} with the nucleophile concentration (Figs 3 and 6) indicate this lack of base catalysis at the micellar pseudophase. These are expected results considering that the micellar interfaces are more polar than the organic medium,[29] where the reactions are not base catalyzed either.

Also, as shown previously,[14,15] there is no evidence of amine protonation in the reverse micellar systems used in this work, and this possibility is considered negligible. The rate of the reaction can be expressed by

$$\frac{d[P]}{dt} = -\frac{d[FNBA]}{dt} = k'_b \frac{[PIP_b][FNBA]}{\bar{v}[Surf]} \qquad (4)$$

For absolute comparison of reactivities in different media, the molar reaction volume at the interface, $\bar{v}$ should be known. This can be estimated from the molar volume of AOT and BHDC in the reverse micelles, which can be taken as $\bar{v}$.[15] Hence k'_b is the conventional intrinsic second-order rate constant in the interface. The concentrations in square brackets refer to the total volume of the reverse micelle.

The distribution constant of PIP can be expressed by the equation 5.[5]

$$K_A = \frac{[PIP_b]}{[PIP_f][Surf]} \qquad (5)$$

A simple mass balance using the distribution constant K_A and the analytical concentration of PIP, $[PIP_T]$, allows the calculation of $[PIP_b]$:

$$[PIP_b] = \frac{K_A[Surf][PIP_T]}{(1 + K_A[Surf])} \qquad (6)$$

If $[PIP_T] \gg [FNBA]$, a pseudo-first-order behavior for the kinetics of the reaction is assumed. Then, replacing [FNBA] and $[PIP_b]$ in Eqn (4), we can obtain the final expression for the rate [Eqn (7)] and k_{obs} [Eqn (8)]:

$$\frac{d[P]}{dt} = -\frac{d[FNBA]}{dt} = k_{obs}[FNBA] \qquad (7)$$

with

$$k_{obs} = \frac{(k'_b K_A[PIP_T]/\bar{v})}{(1 + K_A[Surf])} \qquad (8)$$

This equation is valid only when the surfactant concentration is high enough in order to ensure that all the substrate is anchored to the micellar pseudophase. From Figs 2 and 5, it can be seen that for $[Surf] > 0.02$ M, k_{obs} is practically independent of surfactant concentration. These results confirm whole substrate incorporation in the anionic and cationic micellar interfaces at both W_0 values as assumed in Scheme 1. Hence the values of k'_b were calculated using Eqn (8) for $[AOT] > 0.02$ M and the results are given in Table 1. The molar volumes of BHDC and AOT were estimated as 0.44 and 0.38 M^{-1} respectively.[15,30] The values of K_A were calculated in previous work.[14,15]

By introduction of suitable values of K_A, the values of k'_b were recalculated for each system at $W_0 = 0$ and 10 by fitting a different set of experimental data by Eqn (8). The results are compared in Table 1. As can be seen, good estimates for k'_b within experimental error are obtained by two independent methods.

It must be noted that the kinetic profiles obtained at $W_0 = 0$ for both systems [Figs 2(A) and (5)] show a sharp decrease in the rate constant with increasing surfactant concentration. These results can be explained by considering that at low surfactant concentration, both reactants are unevenly distributed between both pseudophases whereas FNBA is incorporated in the micelles where the amine concentration in this region is very low (see the

Table 1. Kinetic parameters and distribution constants for the reaction of FNBA with PIP in different media at 25 °C[e]

System	k'_b ($s^{-1} M^{-1}$)	K_A (M^{-1})[a]
AOT–benzene, $W_0 = 0$	$(3.4 \pm 0.2) \times 10^{-3}$ [b] $(3.8 \pm 0.2) \times 10^{-3}$ [c]	0.09 ± 0.04
AOT–benzene, $W_0 = 10$	$(4.0 \pm 0.3) \times 10^{-2}$ [b] $(3.4 \pm 0.2) \times 10^{-2}$ [c]	0.10 ± 0.04
BHDC–benzene, $W_0 = 0$	$(1.8 \pm 0.2) \times 10^{-3}$ [d] $(1.9 \pm 0.2) \times 10^{-3}$	0.3 ± 0.1
BHDC–benzene, $W_0 = 10$	$(7.8 \pm 0.3) \times 10^{-3}$ [d] $(6.9 \pm 0.3) \times 10^{-3}$	0.3 ± 0.1

[a] From Ref. 15.
[b] From Fig. 2, calculated by Eqn (8) for $[AOT] > 0.02$ M.
[c] From fitting of Fig. 3 by Eqn (8).
[d] From Fig. 5, calculated by Eqn (8) for $[BHDC] > 0.02$ M.
[e] From fitting Fig. 6 by Eqn (8). Parameter values calculated using 0.995 confidence level in non-linear regression.

value of K_A in Table 1). For both systems, at [Surf] > 0.02 M the reaction takes place only at the interface of the aggregate.

On the other hand, the value of k'_b in AOT–benzene is twice that BHDC–benzene (Table 1), reflecting the higher micropolarity of the AOT than the BHDC interface.[29] Surprisingly, the reaction is slower at these interfaces than in benzene and water because it may take place near the oil side of the reverse micelle interface, away from the residual water and the counter ions.

The kinetic behavior obtained at $W_0 = 10$ [Figs 2(B) and 5] in both micellar systems is different, showing the different influences that the anionic and cationic interfaces have in the reaction. There is an important increment in the reaction rate with increasing AOT concentration. At [AOT] > 0.02 M, the values obtained are higher than that found in pure water (Table 1). Since FNBA is negatively charged, it may be pushed towards the water side of the interface, by the anionic heads of AOT and where the counterions are located. Considering that this rate enhancement could be an effect of the ionic strength of the interface, the value of the reaction rate was correlated with the corresponding values in water at different ionic strength [Fig. 1(B)]. From this comparison it can be inferred that the average ionic strength inside the reverse micelles is around 4.7 M. Similar values were assumed for AOT–isooctane reverse micelle systems.[31] It seems that the negative charged intermediate $\mathbf{Z_b}$ is located at the water side of the interface sensing the average ionic strength of the microenvironment. In contrast, with increase in [BHDC] a small effect on the rate constant is observed similar to that obtained in pure benzene (Table 1). In this case, the $\mathbf{Z_b}$ intermediate could be anchored to the cationic interface and the reaction occurs mostly at the oil side.

In both systems, the addition of water (W_0) produces an increase in the reaction rate (Figs 4 and 7), reflecting the enhancement of the interface micropolarity by the addition of water.[29]

CONCLUSIONS

The reaction of FNBA with PIP is not base catalyzed either in homogeneous media or in the micellar systems studied. In water, the reaction is faster than in benzene, probably owing to the better stabilization of the **Z** intermediate transition state in the more polar solvent. Also, the reaction rate in water is accelerated by the addition of salt. These properties are used to characterize the micellar systems studied, benzene–AOT–water and benzene–BHDC–water. The reaction rates are practically independent of the surfactant concentration above 0.02 M, indicating the complete incorporation of FNBA as carboxylate in the micellar pseudophase where the reaction takes place. When water is not added, i.e. $W_0 = 0$, there is a sharp decrease in the reaction rate with increasing surfactant concentration, reflecting the different location of the substrate and the nucleophile. However, at $W_0 = 10$ the reaction rates present a different situation. In the BHDC system, the reaction rate increases in comparison with $W_0 = 0$ reaching a similar value to that in benzene. It seems that the **Z** intermediate is anchored at the oil side of the cationic interface not sensing the water. On the other hand, the reaction in the AOT system shows an important increase in the reaction rate, being 10 times faster than in benzene and even faster than in pure water. Under this condition the reaction rate is similar to that obtained in water at an ionic strength of 4.7. In this way, and taking into account that the **Z** intermediate is located in the water region of the interface, it can be deduced that the average ionic strength corresponding to interface of AOT–benzene aggregates is of the order of 4–5 M. This interesting result shows that the average ionic strength of AOT–benzene reverse micelles is similar to that obtained in isooctane or hexane–AOT–water systems.

EXPERIMENTAL

General. UV–visible spectra were recorded on a Hewlett-Packard HP 8453 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra and mass spectra were recorded on a Bruker 200 MHz spectrometer and Micromass ZAB-SEQ instrument, respectively. Silica gel thin-layer chromatographic (TLC) plates (250 μm) from Aldrich were used.

Materials. 4-Fluoro-3-nitrobenzoic acid (FNBA) from Aldrich and piperidine (PIP) from Riedel-de Haën were used without further purification. Sodium bis(2-ethylhexyl)sulfosuccinate (AOT) from Sigma (purity > 99%) was used as received. The UV–visible spectra of 1-methyl-8-oxyquinolinium betaine in the presence of AOT reverse aggregates in benzene showed that the surfactant was free of acidic impurities.[32] It was kept under vacuum over P_2O_5 until it was used. Benzyl-*n*-hexadecyldimethylammonium chloride (BHDC) from Sigma was recrystallized twice from ethyl acetate and dried under vacuum over P_2O_5.[29] Benzene (Sintorgan, HPLC quality) was used as received. Ultrapure water was obtained from a Labonco Model 90901-01 system.

Procedures. Stock solutions of surfactant reverse micelles were prepared by weighing and dilution in benzene. Stock solutions of 0.5 M surfactant were agitated in a sonicating bath until the reverse micelle was optically clear. The appropriate amount of stock solution to obtain a given concentration of surfactant in the micellar media was transferred into the cell. The addition of water to the corresponding solution was performed using a calibrated microsyringe. The amount of water present in the system is expressed as the molar ratio between water and the surfactant present in the reverse micelle ($W_0 = [H_2O]/$

[surfactant]). The lowest value of W_0 ($W_0 = 0$) corresponds to a system with no addition of water and the presence of water corresponds to the intrinsic humidity of the system ($W_0 \approx 0.3$).

Kinetics. Reactions were followed spectrophotometrically by measuring the increase in the maximum absorption band of the product, *N*-(2-nitro-4-carboxyphenyl) piperidine, at 25.0 ± 0.5 °C. To start a kinetic run, a stock solution of FNBA was added (10 µl) to a thermostated cell containing the PIP and the reverse micelle solution. The FNBA concentration in the reaction media was 1.5×10^{-4} M. The kinetic runs were performed by following the increase in the absorbance of the product of the reaction ($\lambda_{max} = 434$ nm). In every case, pseudo-first-order plots were obtained in excess of nucleophile. The pseudo-first-order rate constants (k_{obs}) were obtained by a non-linear least-squares fit of the experimental data of absorbance vs time, ($r > 0.999$) by a first-order rate equation. The value of the absorbance at infinite reaction time was consistent with the value obtained from authentic samples of the reaction product, within 3%. The pooled standard deviation of the kinetic data, using different prepared samples, was < 5%.

Synthesis of the product. FNBA (57 mg, 0.308 mmol) was stirred with PIP (500 µl, 5.88 mmol) in tetrahydrofuran (5 ml) for 24 h at room temperature. The reaction mixture was partitioned between water and dichloromethane–methanol (10%) and neutralized with HCl. The volatiles of the organic phase were evaporated under vacuum and afforded 74 mg (96%) of pure product. TLC (silica gel), R_F (dichloromethane–methanol, 10%) = 0.42. ^{1}H NMR (DMSO-d_6, TMS), δ (ppm): 1.48 (m, 6H, CH_2); 3.01 (t, 4H, CH_2, $J = 5.0$ Hz); 7.29 (d, 1H, Ar, $J = 9.1$ Hz); 7.98 (dd, 1H, Ar, $J = 2.2$, 8.8 Hz); 8.25 (d, 1H, Ar, $J = 2.2$ Hz); 9.80 (br, 1H, COOH). FAB-MS: *m/z* 250 (M^+) (250.0954 calculated for $C_{12}H_{14}N_2O_4$).

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